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Securing Your Health

Avipiravir

Special warning and precaution for use

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- Do not prescribe the drug to women known or suspected to be pregnant, as early embryonic deaths and teratogenicity have been observed in animal studies for Avipiravir.

Special warning and precaution for use

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- A pregnancy test should be performed and should be negative before starting the treatment when administering Avipiravir to women of child-bearing potential. You should explain the full risks and instruct thoroughly to use most effective contraceptive methods with her partner during treatment and for 7 days after the end of the treatment. You should advice patient to discontinue the treatment immediately and to consult a doctor if pregnancy is suspected while taking this medication.

Special warning and precaution for use

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- Since Avipiravir transfers to semen, and this full risks should have explained sufficiently when administering the drug to male patients, and should advise them to use most effective contraceptive methods in sexual intercourse during the treatment and for 7 days after the end of the treatment (men should wear a condom). In addition, instruct not to have sexual intercourse with pregnant women during this period.

Special warning and precaution for use

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- Prior to the treatment commencement, efficacy and risks (including the risk of exposure to fetus) should be fully explained in written form to patients or their family members, etc.
- Administration should be started after obtaining their written consent.
- Examine carefully the necessity of Avipiravir before use.

Contraindications

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- Pregnant women or who may be pregnant (Early embryonic deaths and teratogenicity have been observed in animal clinical studies).

- Patients with a history of hypersensitivity to any ingredient of the drug.

Adverse Events

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Avipiravir has never been administered with the approved dosage. In Japanese clinical studies and the global phase III of the study (studies conducted with dose levels lower than the approved dosage), side effects were observed in 100 of 501 patients (19.96%) evaluated for the safety (including abnormal laboratory test values).

Adverse Events

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- Major side effects were:

1. Increase of blood uric acid level in 24 patients (4.79%)
2. Diarrhea in 24 patients (4.79%)
3. Decrease of neutrophil count in 9 patients (1.80%)
4. Increase of AST (GOT) in 9 patients (1.80%)
5. Increase of ALT (GPT) in 8 patients (1.60%).

Serious Side Effects

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Abnormal behavior (frequency unknown):

- Although the causal relationship is unknown, abnormal behavior (e.g. suddenly running, wandering around) leading to falls etc., may occur in patients with influenza virus infection.

Serious Side Effects

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- The following serious side effects have been reported with other anti-influenza virus drugs. Therefore, patients should be carefully monitored, and if any abnormality is observed, the treatment should be stopped and appropriate measures should be taken.

- **Shock, anaphylaxis.**
- **Pneumonia.**
- **Hepatitis fulminant, hepatic dysfunction, jaundice.**
- **Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome).**

Serious Side Effects

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- **Acute kidney injury.**
- **White blood cell count decreased, neutrophil count decreased, platelet count decreased.**
- **Neurological and psychiatric symptoms (consciousness disturbed, deliria, hallucination, delusion, convulsion, etc.).**
- **Hemorrhagic colitis.**

Use in hepatic impairment

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- When Favipiravir was orally administered to patients with mild and moderate liver dysfunction (Child-Pugh classification A and B, 6 patients each) at 1200 mg twice daily for 1 day followed by 800 mg twice daily for 4 days (1200 mg/800 mg twice per day) [Note 9], compared to healthy adult patients, C_{max} and AUC at day 5 were approximately 1.6 fold and 1.7 fold, respectively in patients with mild liver dysfunction, and 1.4 fold and 1.8 fold, respectively in patients with moderate liver dysfunction.

Use in hepatic impairment

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- When Favipiravir was orally given to patients with severe liver dysfunction (Child-Pugh classification C, 4 patients) at 800 mg twice daily for 1 day followed by 400 mg twice daily for 2 days (800 mg/400 mg twice per day) [Note 9], compared to healthy adult patients, C_{max} and AUC at day 3 were approximately 2.1 fold and 6.3 fold, respectively

Use in elderly

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- In general, elderly patients often have reduced physiological functions, so Avipiravir should be given with care to them and monitoring their general conditions.

Use in Diabetics

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- Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycemia, after initiating direct-acting antiviral treatment.
- Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated.

Interactions with other products

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- Avipiravir is not metabolized by cytochrome P-450 (CYP), but mainly metabolized by aldehyde oxidase (AO), and partly metabolized by xanthine oxidase (XO). It also inhibits AO and CYP2C8, but does not induce CYP.

Interactions with other products

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Drug Interactions:

Avipiravir is not metabolized by cytochrome P-450 (CYP), but mainly metabolized by aldehyde oxidase (AO), and partly metabolized by xanthine oxidase (XO). It also inhibits AO and CYP2C8, but does not induce CYP.

Precautions for co-administration

(Avipiravir should be administered with care when co-administered with the following drugs):

Drugs Name	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Pyrazinamide	Blood uric acid level increases. When pyrazinamide 1.5g once daily and Avipiravir 1200 mg /400 mg twice daily were administered, the blood uric acid levels were 11.6 mg/dL when pyrazinamide was administered alone, and 13.9 mg/dL in combination with Avipiravir.	Reabsorption of uric acid in the renal tubule is additively promoted.
Repaglinide	Blood level of Repaglinide may be increased, and side effects to Repaglinide may be occurred.	Inhibition of CYP2C8 increases blood level of Repaglinide.
Theophylline	Blood level of Avipiravir may be increased, and side effects to Avipiravir may be occurred.	Interaction with XO may increase blood level of Avipiravir.
Famciclovir Sulindac	Efficacy of these drugs may be reduced.	Inhibition of AO by Avipiravir may decrease blood level of active forms of these drugs.

Use in Pregnancy

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- Do not give Avipiravir to pregnant women or a woman who suspected to be pregnant.
- (Early embryonic deaths [rats] and teratogenicity [monkeys, mice, rats and rabbits] have been observed in animal studies with exposure levels similar to or lower than the clinical exposure)

Use in Lactation

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- If Avipiravir is given to lactating women, instruct them that they should stop lactating.
- (The major metabolite of Avipiravir, a hydroxylated form, was found to be passed in breast milk).

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Avipiravir in COVID-19

Study design

This was a multi-center, randomized, interventional phase2/ phase3 study that included 96 patients with confirmed SARS-CoV-2 infection. This study was performed at the Ain-Shams University and Tanta University hospitals in the period from April to August 2020.

Study design:

- 48 patients who received Chloroquine 600 mg tablets twice daily added to the standard-of-care therapy for 10 days
- The Favipiravir group included 48 patients who received 1600 mg of Favipiravir twice a day on the first day and 600 mg twice a day from the second to tenth day, added to the standard-of-care therapy for 10 days

The two groups were compared in terms of:

- Time to SARS-CoV-2 negativity
- Duration of hospital stays

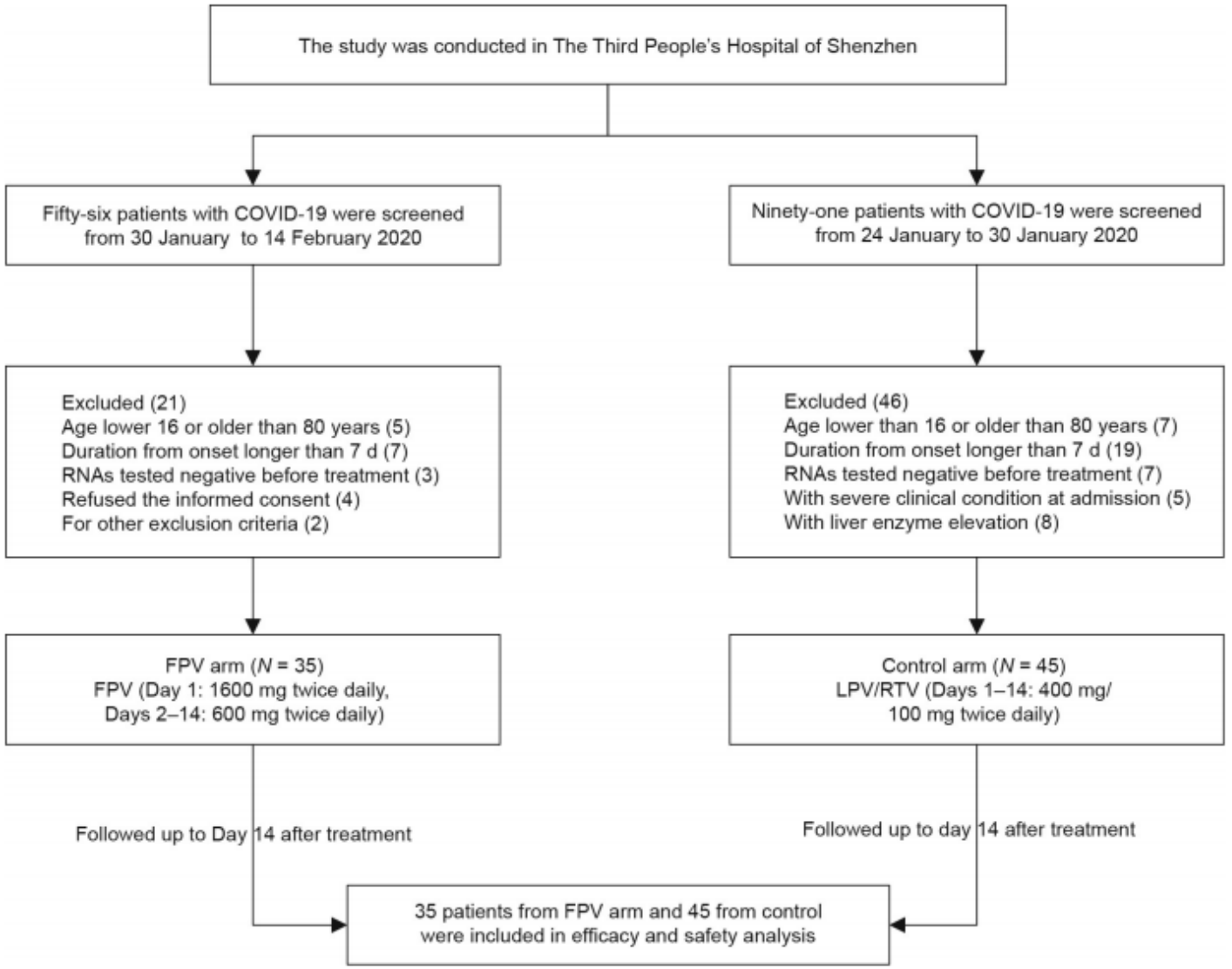
Efficacy of Favipiravir in COVID-19 treatment: a multi-center randomized study Archives of Virology https://doi.org/10.1007/s00705-021-04956-9

Results

- the Favipiravir group had a lower mean duration of hospital stay (13.29 ± 5.86 days) than the CQ group (15.89 ± 4.75 days).
- None of the patients in the Favipiravir group needed mechanical ventilation or had an oxygen saturation lower than 90
- Favipiravir is a promising drug for treatment of COVID-19 that might decrease the hospital stay and the need for mechanical ventilation

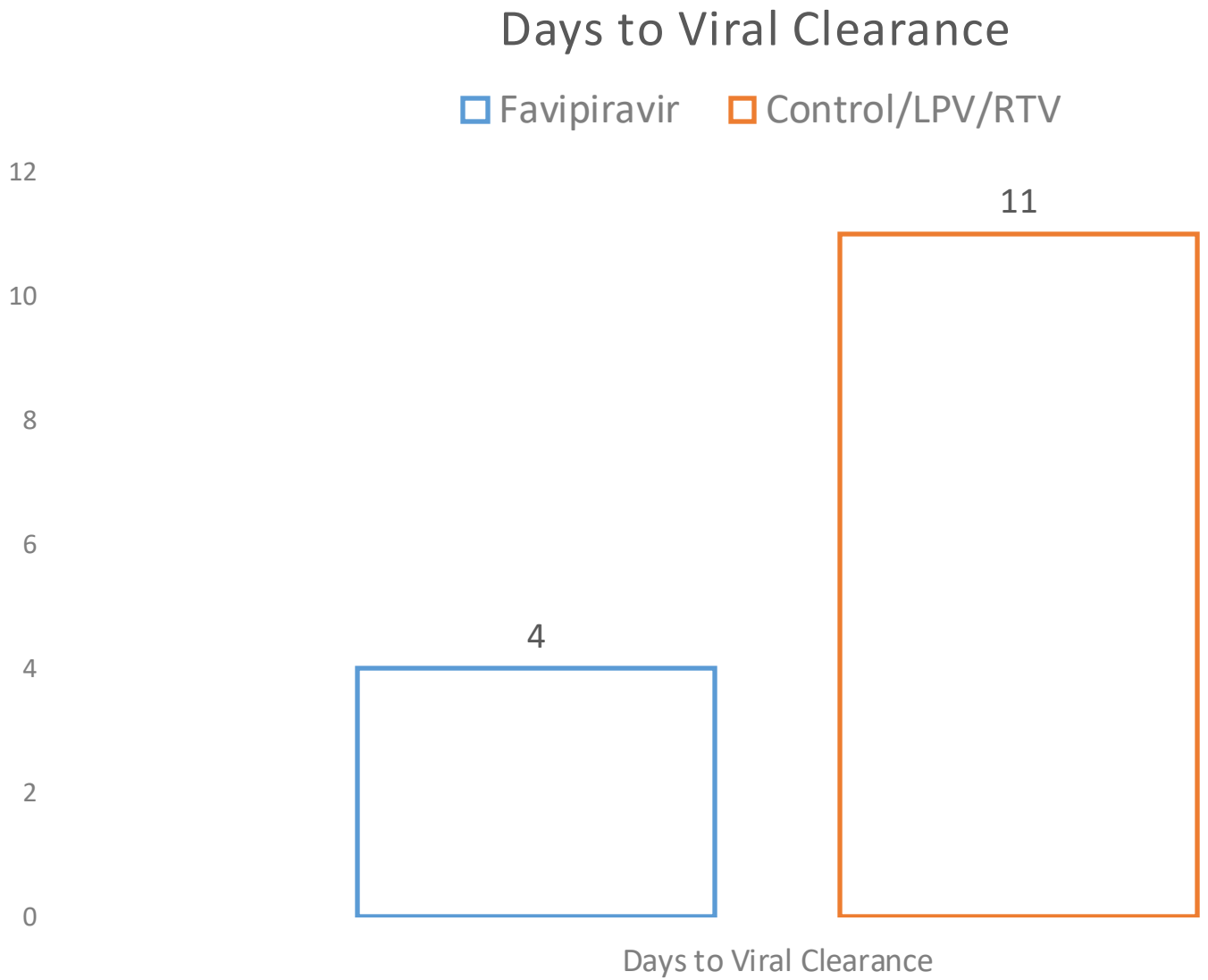
Efficacy of Favipiravir in COVID-19 treatment: a multi-center randomized study Archives of Virology https://doi.org/10.1007/s00705-021-04956-9

Study design



Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study a National Clinical Research Center for Infectious Diseases, The Third People's Hospital of Shenzhen, The Second Affiliated Hospital of Southern University of Science and Technology, Shenzhen 518100, China b National Engineering Research Center for the Emergence Drugs, Beijing Institute of Pharmacology and Toxicology, Beijing 100850, China

Results



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Results

- The median time of viral clearance for the patients treated with FPV, designated as Group A, was estimated to be 4 d (IQR: 2.5–9), which was significantly shorter than the time for patients in the control group, designed as Group B, which was 11 d (IQR: 8–13) ($P < 0.001$)

- In this open-label comparative controlled study of patients with COVID-19, those treated with FPV appeared to have faster viral clearance and better chest imaging change than patients treated with LPV/RTV.

Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study a National Clinical Research Center for Infectious Diseases, The Third People's Hospital of Shenzhen, The Second Affiliated Hospital of Southern University of Science and Technology, Shenzhen 518100, China b National Engineering Research Center for the Emergence Drugs, Beijing Institute of Pharmacology and Toxicology, Beijing 100850, China

Study design

This was an adaptive, multicenter, open label, randomized, Phase II/III clinical trial of Favipiravir versus standard of care (SOC) in hospitalized patients with moderate COVID-19 pneumonia in April and May 2020

Study design:

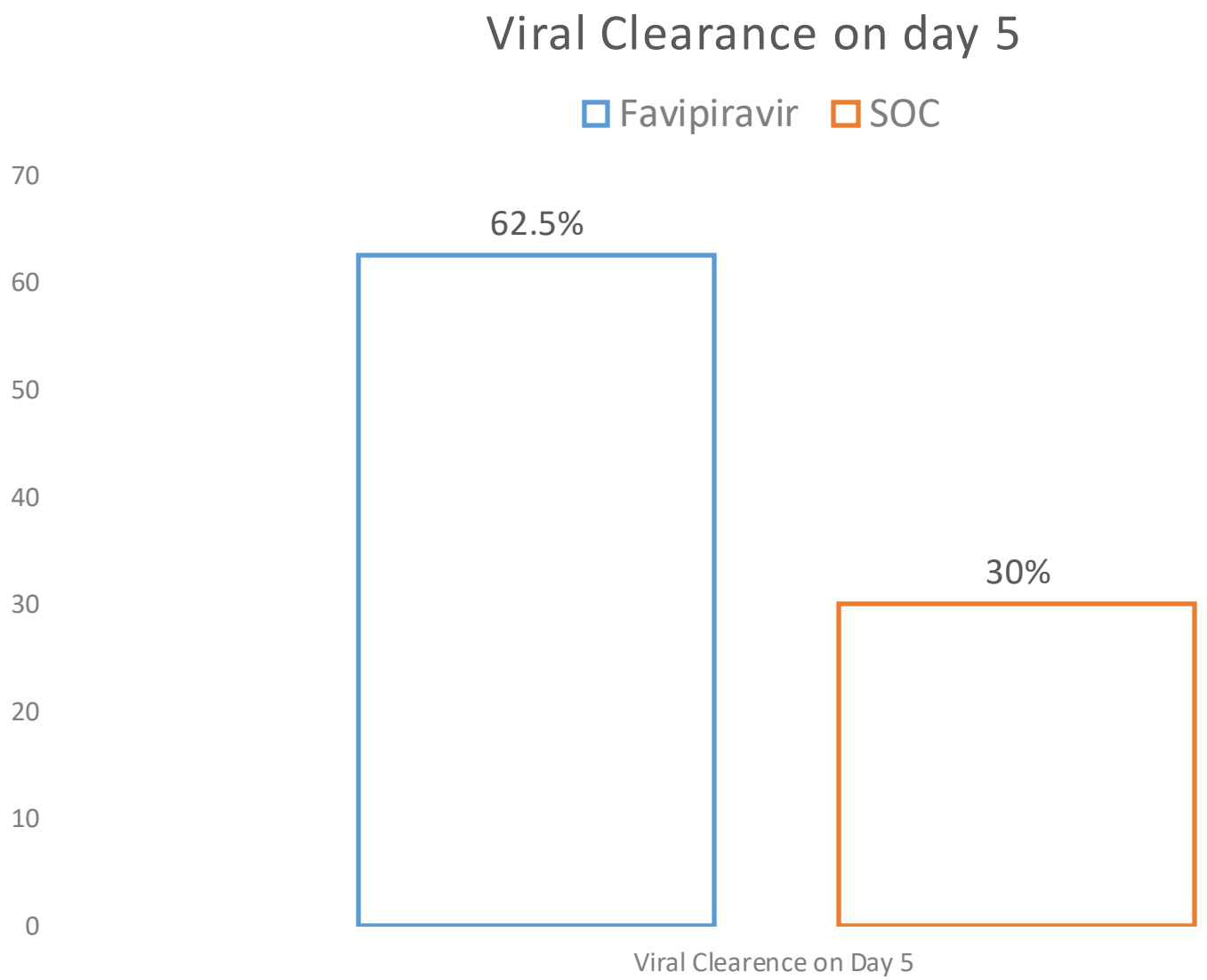
- The patients were randomized at a 1:1:1 ratio to receive either Favipiravir 1600 mg BID on Day 1 followed by 600 mg BID on Days 2-14 (1600/600 mg)
- Favipiravir 1800 mg BID on Day 1 followed by 800 mg BID on Days 2-14 (1800/800 mg)
- SOC according to the Russian guidelines for treatment of COVID-19

The two groups were compared in terms of:

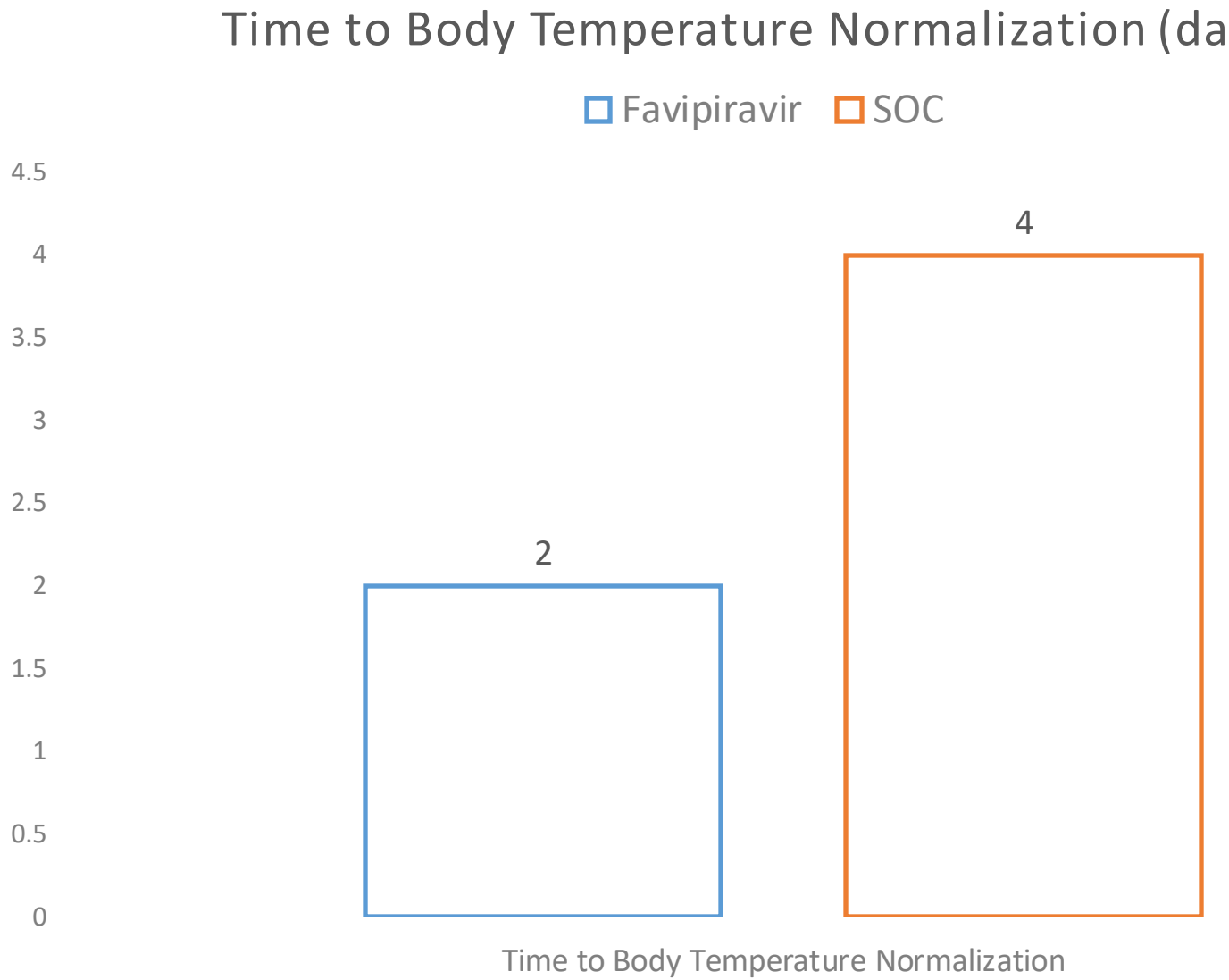
- Time to SARS-CoV-2 negativity
- Duration of hospital stays

2- Andrey A. Ivashchenko, et al. AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. medRxiv. August 5, 2020.

Results



Results



Results

- Both dosing regimens of Favipiravir demonstrated similar virologic response.
- On Day 5, the viral clearance was achieved in 25/40 (62.5%) patients on Favipiravir and in 6/20 (30.0%) patients on SOC (p=0.018).
- The median time to body temperature normalization (< 37₀ C) was 2 days (IQR 1-3) in the AVIFAVIR groups and 4 days (IQR 1-8) in the SOC group (p=0.007).
- By Day 10 the viral clearance was achieved in 37/40 (92.5%) patients on Favipiravir and in 16/20 (80.0%) patients on SOC (p=0.155).

2- Andrey A. Ivashchenko, et al. AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. medRxiv. August 5, 2020.

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Mechanism of Action in COVID-19

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✓Favipiravir is metabolized in cells to a ribosyl triphosphate form (Favipiravir RTP) and that Favipiravir RTP selectively inhibits RNA polymerase involved in influenza viral replication.